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STEVEN F. WEINSTOCK
ABBOTT LABORATORIES
100 ABBOTT PARK ROAD
DEPT. 377/AP6A
ABBOTT PARK, IL 60064-6008

| EXAMINER | |
|---|---|
| FREDMAN, JEFFREY NORMAN | |
| ART UNIT | PAPER NUMBER |
| 1634 | |

DATE MAILED: 03/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/922,277 | KATZ, DAVID A. | |
| | Examiner | Art Unit | |
| | Jeffrey Fredman | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *19-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Status*

This action is supplemental to the non-final action mailed February 3, 2003. That action, inadvertently in paragraph 10, stated that claim 14 was again rejected, instead of claims 17 and 18 as the action should have indicated. This has been corrected. Applicant's time period will begin from the mailing of the current action, not the earlier action.

### *Election/Restrictions*

1. Applicant's election with traverse of Group I, claims 1-18, in Paper No. 5 is acknowledged. The traversal is on the ground(s) that there is not an undue burden to search both groups. This is not found persuasive because the separate classification is prima facie evidence of burden, which has not been rebutted. Further the search and consideration of the two groups is likely to result in different art being applied, different search terms used and different issues for consideration, all of which represents a burden on examination.

The requirement is still deemed proper and is therefore made FINAL.

### *Claim Rejections - 35 USC § 102*

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1, 6-9, 11, 13, 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Ruano et al. (Proc. Natl. Acad. Sci. (1990) 87:6296-6300).

Ruano et al teach a method of identifying the haplotype of an organism (see abstract), the method comprising:

(a) providing a sample comprising either genomic nucleic acids or PCR amplified nucleic acids from the organism, wherein the nucleic acids comprise at least two copies of an isogenic nucleotide sequence of interest (See page 6297, columns 1 and 2, subheadings "Dilutions"),

(b) aliquotting the nucleic acids into test locations such that at least one test location would be expected to contain one, and only one, isogenic nucleotide sequence of interest (page 6297, columns 2, "36.8% would be expected to contain a single molecule"),

(c) amplifying the isogenic nucleotide sequence of interest in a predetermined number of test locations to create amplification products (page 6297, column 1, "Booster PCR")

(i) wherein amplifying the isogenic nucleotide sequence of interest employs two pairs of oligonucleotide primers (see page 6300, column 1, "If diluted DNA exists as relatively large fragments, distant segments in an intact template molecule are amenable to PCR with multiple primer pairs for direct haplotype determination.")

(ii) such that at least one test location is expected to contain amplification products having a unique nucleotide sequence corresponding to the nucleotide sequence of one and only one of the isogenic nucleotide sequences of interest in the

organism's genome (see page 6298, column 2, "Thus, a heterozygous sample was rendered hemizygous by dilution"),

(d) detecting the presence or absence of specific forms of a first and second nucleotides of interest at two non-contiguous positions in the nucleotide sequence of interest by detecting the presence or absence of each of the polymorphisms such that the haplotype of the organism is determined (see page 6297, column 2 and page 6300, column 1).

Ruano teaches separation of the regions by 3.1 kb, which is about 5 kb (see page 6298, figure 1).

Ruano teaches the use of ASO probes to detect the haplotypes (see page 6298, figure 1).

Ruano shows the use of arrays (see figures 2-4).

Ruano teaches formation of an array using a reagent jetting system (see page 6297, subheading Dot blots, where the array is formed by spotting onto a nylon membrane using a Mini-Fold apparatus, where the spot is dropped using a pipetman type device, which "jets" the reagent into the manifold).

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 2-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al. (Proc. Natl. Acad. Sci. (1990) 87:6296-6300) as applied to claims 1, 6-9, 11, 13, 15 and 16 and further in view of Stephens et al (Am. J. Hum. Genet. (1990) 46:1149-1155).

Ruano et al teach a method of identifying the haplotype of an organism (see abstract), the method comprising:

(a) providing a sample comprising either genomic nucleic acids or PCR amplified nucleic acids from the organism, wherein the nucleic acids comprise at least two copies of an isogenic nucleotide sequence of interest (See page 6297, columns 1 and 2, subheadings "Dilutions"),

(b) aliquotting the nucleic acids into test locations such that at least one test location would be expected to contain one, and only one, isogenic nucleotide sequence of interest (page 6297, columns 2, "36.8% would be expected to contain a single molecule"),

(c) amplifying the isogenic nucleotide sequence of interest in a predetermined number of test locations to create amplification products (page 6297, column 1, "Booster PCR")

(i) wherein amplifying the isogenic nucleotide sequence of interest employs two pairs of oligonucleotide primers (see page 6300, column 1, "If diluted DNA exists as relatively large fragments, distant segments in an intact template molecule are amenable to PCR with multiple primer pairs for direct haplotype determination.")

(ii) such that at least one test location is expected to contain amplification products having a unique nucleotide sequence corresponding to the nucleotide sequence of one and only one of the isogenic nucleotide sequences of interest in the organism's genome (see page 6298, column 2, "Thus, a heterozygous sample was rendered hemizygous by dilution"),

(d) detecting the presence or absence of specific forms of a first and second nucleotides of interest at two non-contiguous positions in the nucleotide sequence of interest by detecting the presence or absence of each of the polymorphisms such that the haplotype of the organism is determined (see page 6297, column 2 and page 6300, column 1).

Ruano teaches separation of the regions by 3.1 kb, which is about 5 kb (see page 6298, figure 1).

Ruano teaches the use of ASO probes to detect the haplotypes (see page 6298, figure 1).

Ruano shows the use of arrays (see figures 2-4).

Ruano does not teach the use of dilutions where the Poisson distribution would yield less than about 1 copy of the isogenic region of interest per location.

Stephens teaches that the concentration is a results optimizable variable which can be adjusted to maximize success of haplotyping by balancing the efficiency of the PCR with the need to dilute the target to a single haplotype (see page 1150, table 1 and page 1152, column 2). Stephens shows that the optimal range for the haplotype equivalents is around 0.6 (see figure 3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the single molecule haplotyping method of Ruano to maximize the probability of a successful experiment as taught by Stephens (who is a collaborator of Ruano) since Stephens states "Clearly, P(Sx) is maximized at about 10 vials for DNA concentrations in the range of 0.6-2.6 and breakage less than 15% (page 1152, column 2)". An ordinary practitioner would have been motivated, by this express statement of optimal amounts, and by the showing in figure 3 that 0.6 is about an optimal amount of copies for the Ruano method, to use about 0.6 copies in each test location in the Ruano method.

7. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al. (Proc. Natl. Acad. Sci. (1990) 87:6296-6300) as applied to claims 1, 6-9, 11, 13, 15 and 16 and further in view of Backman et al (EP 320308).

Ruano teaches the limitations of claims 1, 6-9, 11, 13, 15 and 16 as discussed above. Ruano does not teach the use of alternate methods of amplification such as ligase chain reaction.

Backman teaches the use of ligase chain reaction for detection of nucleic acids (see column 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the single molecule haplotyping method of Ruano to utilize ligase chain reaction for detection since Backman states "The use of this method is particularly advantageous when the target sequence is present in low levels (see column 1, lines 39-41)". An ordinary practitioner would have recognized that in using the method of Ruano, where the target sequence is at very low levels, the method of Backman would be advantageous in detecting the presence or absence of the target nucleic acid.

8. Claims 5, 10 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al. (Proc. Natl. Acad. Sci. (1990) 87:6296-6300) as applied to claims 1, 6-9, 11, 13, 15 and 16 and further in view of Tyagi et al (U.S. Patent 6,037,130).

Ruano teaches the limitations of claims 1, 6-9, 11, 13, 15 and 16 as discussed above. Ruano does not teach the use of alternate methods of amplification nor the use of molecular beacon probes.

Tyagi teaches the use of molecular beacon probes (see column 1, lines 14-30). Tyagi further teaches a variety of modes of amplification as equivalent including PCR, NASBA, TMA, LCR and QB replicase mediated amplification (see column 5, lines 47-55). Tyagi teaches that the type of DNA used in the method can be varied (see column 4, lines 57-59).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the single molecule haplotyping method of Ruano to utilize the alternate methods of amplification and alternate nucleic acid targets as taught by Tyagi since the methods are known equivalents to PCR and cDNA is a known equivalent target to mRNA or genomic DNA. As MPEP 2144.06 notes "An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)." Here, the claimed amplification methods are expressly indicated by Tyagi to be equivalent to the PCR method and would be equivalent in the use of amplifying nucleic acids. It would have further been prima facie obvious to apply the method of Ruano to use Molecular beacon probes since Tyagi states "For some molecular beacon probes, which we refer to as "allele discriminating" only perfectly complementary strands are targets that cause this change under assay conditions (see column 4, lines 41-44)". An ordinary practitioner would have been motivated to use an allele discriminating molecular beacon of Tyagi in the method of Ruano in order to sensitively and specifically determine the haplotype in real time.

9. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al. (Proc. Natl. Acad. Sci. (1990) 87:6296-6300) as applied to claims 1, 6-9, 11, 13, 15 and 16 and further in view of Vogelstein et al (Proc. Natl. Acad. Sci. (1999) 96:9236-9241).

Ruano teaches the limitations of claims 1, 6-9, 11, 13, 15 and 16 as discussed above. Ruano does not teach the use of wells of multiwell plates for single molecule dilution.

Vogelstein teaches the use of wells of multiwell plates for single molecule dilution assays. (see page 9236, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Ruano to use multiwell plates as taught by Vogelstein since Vogelstein teaches that "The limit of detection is defined by the number of wells that can be analyzed and the instrinsic mutation rate of the polymerase used for amplification. The 384-well PCR plates are commercially available and 1,536 well plates are on the horizon (see page 9239, column 2)". An ordinary practitioner would have been motivated to use the multi-well plates of Vogelstein to extend the limit of detection of Ruano by permitting greater dilution to ensure that the molecules were actually single molecules and not multiple molecules, since the limit of accuracy on the Ruano method is also the number of samples analyzed relative to the dilution rate of the method.

10. Claims 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al. (Proc. Natl. Acad. Sci. (1990) 87:6296-6300) as applied to claims 1, 6-9, 11, 13, 15 and 16 and further in view of Krynetski et al (Proc. Natl. Acad. Sci. (1995) 92:949-953).

Ruano teaches the limitations of claims 1, 6-9, 11, 13, 15 and 16 as discussed above. Ruano does not teach haplotyping of the TPMT gene.

Krynetski teaches that there are two haplotypes in the TPMT gene, one of which is associated with cytotoxicity in chemotherapeutic treatment using methylmercaptopurine including the specific haplotypes of claim 18 (see page 949, columns 1 and 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of Ruano to haplotype the TPMT gene since Krynetski teaches "Identification of the inactivating mutations at the TPMT locus would not only provide important insights into the molecular mechanisms of this genetic polymorphism but might also offer a method of prospectively identifying heterozygotes and TPMT-deficient patients prior to treatment with potentially toxic dosages of mercaptopurine (page 949, column 2)". Thus, an ordinary practitioner would have been motivated to haplotype the TPMT gene using the method of Ruano in order to diagnose patients who are TPMT deficient prior to toxic treatment.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

March 28, 2003